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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,677	05/16/2006	Yingfu Li	16554-005US1H310899PCTUS	3072

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
09/15/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

INFO@ORTPATENT.COM

Office Action Summary	Application No.	Applicant(s)	
	10/562,677	LI ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-21* is/are pending in the application.

4a) Of the above claim(s) *4,7,9,15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5, 6, 8,10-14,16-18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of (1) "an increase in the amplitude of the signal," (2) "an addition of a functional group," (3) a phosphatase, (4) AMP being the substrate, and (5) "increase in signal intensity" in the reply filed on 6/2/08 is acknowledged.

Applicant states Claims 1-3, 5-7, 10-14, 16-18, 20, and 21 are readable on the elected species. (The Examiner notes claim 2 was cancelled at least as of 5/16/06.

During a telephone conversation with Attorney for Applicant, Jenny Chen, on 9/9/08 a provisional election was made to prosecute the invention of claim 8 (removal of a functional group), not claim 7 (addition of a functional group) as originally elected in the response. The corrected election is in keeping with the elections of a phosphatase and AMP. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 1 and 3-21 are pending.

Accordingly, Claims 4, 7, 9, 15, and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim.

Claims 1, 3, 5, 6, 8, 10-14, 16-18, 20, and 21 are examined herein.

Claim Objections

Claim 1 is objected to because it contains two, sentence-ending periods. Pursuant to MPEP 608.01(m) each claim should end with a period, but periods should not be used elsewhere except in abbreviations. Appropriate correction is required.

Claims 5 is objected to because of the recitation "afluorophore." A space is needed between 'a" and "fluorophore."

Claim 13 is objected to because of the recitation "has a different affinities." Applicant will note the grammar is awkward.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The U.S. Court of Appeals Federal Circuit decision in *Pfizer Inc. v. Teva Pharmaceuticals USA Inc.*, 86 USPQ2d 1001 (Fed. Cir. 2008) makes it clear that the protection afforded by 35 USC 121 applies only to divisional applications filed as the result of a restriction requirement.

Claims 1, 3, 5, 6, 8, 10-14, 16-18, 20, and 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, and 24-35 of copending Application No. 10/502,190 in view of supporting disclosure therein at a pages 26 and 27 and Fig. 2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a signaling aptamer for the detection of a target and that binds to AMP, has a complementary oligonucleotide binding domain, and is bound to a complemenary oligonucleotide comprised of separate molecules having a fluorophore and a quencher such that upon binding of said target to said aptamer said complementary oligonucleotide is released and a fluorescent signal is generated.

MPEP 804 states that "those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)."

Written description support for the invention claimed in the conflicting application shows that a signaling aptamer representative of the invention is one such as that disclosed at Fig. 2 therein, which aptamer is identical to that disclosed for use in the instantly claimed method.

Compare the aptamer in Fig. 1 of 10/562677 with that disclosed in Fig. 2 of 10/502190. Accordingly, species representative of the conflicting inventions are identical.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim interpretation

The claims embrace methods performed in cell-free or homogenous solutions, cells in culture, and in vivo in an animal.

Absent a special meaning in the specification, which, currently, is not found by the Examiner, broadest reasonable interpretation of the term "signal" includes any observable and/or quantifiable change occurring in the sample, cell culture, or animal as a result of an increase or decrease in binding either Substance A or B to the aptamer.

The method of independent claim 1 does not require that a change in signal amplitude occur; the claim simply requires "monitoring for a change."

Claim 1 further does not require the affinity for substance A be lower or higher than the affinity for product B. The claim merely requires the relative affinities be different.

The claim further does not specify any particular relationship between substance A and product B. While using letters A and B implies a direct derivation of B from A, this would be assumption only. Broadest reasonable interpretation includes embodiments wherein the

substance A and product B are indirectly related molecules, wherein product B is produced directly or indirectly from A. For example, B may be produced indirectly from A by any number of additional downstream reactions. The claim does require, however, that substance A be capable of undergoing a modification and that any change in signal be indicative of that modification. One embodiment consistent with the specification is that wherein B is produced directly from A by removal or addition of a functional group.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 7, 10, 13, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Gallivan (US Patent Application Publication 2003/0064931 A1).

Gallivan disclosed aptamer constructs for monitoring and detecting a wide range of enzymatic activities. The aptamer is operably linked to a reporter gene encoding, for example, a fluorescent or toxic protein (paragraph 54). When bound to the preferred ligand, the aptamer may inhibit or enhance the expression of the reporter gene, resulting in a readily detectable signal (cell death or fluorescence) representative of changes in the concentration of the preferred ligand

(paragraphs 61-70). Having high affinity for a first substrate and low or poor affinity for a reaction product of the substrate, the aptamer constructs are said to be useful for the detection of enzyme activities that convert one substance into another, wherein the aptamer preferably binds the precursor molecule but not the product. In the presence of the appropriate enzyme, a reduction in the levels of the precursor molecule results in a detectable signal, such as fluorescence, or, in the case of Examples 1 and 2, beginning at paragraph 78, cell survival. One of skill would recognize many variations of the aptamer constructs as disclosed therein for measuring and detecting enzyme-catalyzed reactions, wherein the signal produced would either decrease or increase depending on the design of the aptamer/expression construct, and whether the aptamer preferably binds the substrate or the product.

Accordingly, Gallivan anticipates the claimed method.

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Claims 1, 3, 5, 6, 10, 13, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Tyagi et al. (1996) *Nat. Biotechnology* 14:303-308.

The claims are interpreted as above.

Additionally, page 9, paragraph 42, the instant specification teaches that "The signaling aptamer may be a molecular beacon as described in Tyagi and Kramer, 1996, incorporated herein by reference."

There is no disclosure or definition in the specification clearly precluding substance A and product B from being nucleic acids. The interpretation is consistent with the specification which teaches using signaling aptamers as real-time probes to report enzyme activities. Enzyme activities reasonably includes DNA polymerase chain reaction amplification of nucleic acids.

Tyagi et al. molecular beacons for monitoring the progress of polymerase chain reaction synthesis of a nucleic acid (page 304-5; Fig. 1). The beacon is designed to preferentially bind the amplification product (Product B). Accordingly, the beacon has highest affinity for the amplified sequence and lower or lowest affinity the trinucleotide (ATP, GTP, CTP, and TTP) precursors (Substance A, B, C, and D), clearly meeting the requirements of claims 1, 3, and 10.

As described at pages 305-308 and shown in Fig. 7, in using molecular beacons to monitor the course of a polymerase chain reaction, Tyagi et al. taught steps for combining molecular beacons with substances A, B, C, and D, enzyme, primers, and buffer, determining the baseline fluorescence, and then monitoring for a change in fluorescence amplitude over time, as measured by the number of cycles. The increase in fluorescence is said to be indicative of binding of the beacon to the amplification product.

With regard to claim 5, the beacon (i.e., aptamer) comprises a quencher and fluorophore in proximity (Fig. 1).

With regard to claim 6, the hairpin-shaped beacon/aptamer comprises an aptamer oligonucleotide (the sequence that binds the amplification product) and quencher oligonucleotide (sequence comprising the quencher) capable of forming duplex with the aptamer oligonucleotide in the absence of an aptamer binding target (Fig. 1).

With regard to claims 13 and 14, by definition, a PCR reaction mixture represents a test sample, and the increase in fluorescene observed in the presence of the molecular beacon indicates the presence of a DNA polymerase, an enzyme.

Accordingly, Tyagi et al. taught every aspect of the instantly claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 6, 8, 10-14, 16-18, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al. (1996) *Nat. Biotechnology* 14:303-308, Gallivan (US Patent Application Publication 2003/0064931 A1), Jhaveri et al. (2000) *J. Am. Chem. Soc.* 122:2469-

2473, Hamaguchi et al. (2001) *Anal. Biochem.* 294:126-131, Li et al. (2002) *Biochem. Biophys. Res. Comm.* 292:31-40.

The claims embrace the use of molecular beacon-like molecules comprising aptameric sequences for real-time detection of analytes produced during a chemical reaction. In some embodiments the reaction is enzyme-catalyzed. In more specific embodiments the enzyme is a phosphatase and the substrate is AMP. Claim 1 does not require the presence of an enzyme.

Tyagi et al. is relied on for the reasons given above. Tyagi et al. taught molecular beacons for real time detection of nucleic acid amplification products.

Li et al. taught molecular aptamer beacons for the real time detection of proteins (pp. 31-40).

Hamuguchi et al. taught molecular aptamer beacons for detecting proteins (pp.126-131). It is suggested the same constructs may be adapted for detection of other chemical compounds (abstract).

Jhaveri et al. taught a molecular beacon-like, adenosine/ATP binding fluorogenic aptamer for the detection of ATP and/or adenosine (Fig. 2b).

In each case cited above, the aptamer comprises quencher and fluorophore in proximity. In each case the references taught steps for incubating the aptamer with substrate and determining the amplitude of the fluorescent signal initially produced thereby. Tyagi et al. further taught monitoring the fluorescence thereafter to follow the progress of the reaction.

Accordingly, it was well known in the prior art that molecular beacons could be adapted for the detection of non-nucleic acid substances in real time in homogenous assays; that molecular beacons were compatible for use with enzyme-catalyzed reactions to detect products produced thereby; and that molecular beacon aptamers could be used to transducer molecular recognition into an optical signal. The prior art taught that to make an molecular aptamer beacon a suitable aptamer sequence may be incorporated into the loop region of the molecular beacon construct taught by Tyagi et al. to produce a ligand-sensitive beacon, which will undergo conformational change upon binding of the ligand to produce a fluorescent signal. For example, see Fig. 1, page 34, in Li et al., showing the typical structure of a molecular aptamer beacon.

Thus, methods for making and using molecular aptamer beacons for virtually any known substance were known in the art.

Accordingly, given that the purpose of said beacons was to detect the presence or absence of a particular analyte in solution, it would have been obvious at the time of invention that such aptamer beacons could be used to monitor the increase in concentration of a given ligand in real time as occurs during the course of an enzyme-catalyzed reaction in the same manner taught and shown by Tyagi et al. to monitor the formation of a nucleic acid sequence during a polymerase-catalyzed polymerization of nucleoside triphosphosphates. Given that the prior art further showed that molecular beacons may be adapted or modified for detection of other substances such as proteins and small molecules, including adenosine or ATP, one of skill would have reasonably predicted that molecular aptamer beacons may be used in a wide variety of assays to detect the formation of any number of substances, as occurs during the course of an enzyme catalyzed reaction.

Given that the prior art cited herein recommended molecular aptamer beacons for their sensitivity and target specificity, one of skill would have been led to use molecular aptamer beacons in diagnostic assays. One such assay is that described by Jhaveri et al. for the detection of adenosine or ATP, known metabolic intermediates of significance to cellular processes. Other assays include the synthesis of proteins or nucleic acids, as taught by Li et al. and Tyagi et al.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
September 9, 2008